REMARKS

Claims 19-40 and 55-65 are pending. Independent claims 19 and 55 have been amended to more clearly point out the invention. Support for the amendments is found in applicants' specification as filed. Support for "sequence comprises the amino acids $X_5X_4X_3X_2X_1$, wherein X_5 is from 0 to 16 amino acids; X_4 is serine, isoleucine, or lysine; X_3 is serine or lysine; X_2 is leucine or lysine; and X_1 is glutamine, asparagine or tyrosine" is found, for example, on page 5, lines 9-20. No new matter is introduced by the claim amendments.

Priority

The claim to the priority of U.S. Application No. 09/081,707 (now U.S. Patent No. 6,265,540) has been properly made.

Rejections Under 35 U.S.C. § 102(b) and 102(a) Over WO 96/00503 to Merck & Co., Inc. and DeFeo-Jones et al. (United States Patent No. 5,599,686)

Claims 19-24, 27-29, 32-37, 55-58, and 61-64 have been rejected as anticipated by Merck. Claims 19-20, 22, 27-29, 32-37, 55-57 and 61-64 have been rejected as anticipated by DeFeo-Jones et al. Applicants respectfully traverse the rejection for the following reasons.

DeFeo-Jones et al. (U.S. Patent No. 5,5,599,686) discloses anti-cancer compositions including oligopeptides based on the sequence of semenogelin I. These oligopeptide-containing compositions can be conjugated with cytotoxic agents so that cleavage by prostate specific antigen (PSA) yields a therapeutic agent. Specific oligopeptides based on the semenogelin I sequence are disclosed (SEQ. ID. NO. 2-6, 10-11, 13-65; column 3, line 31 to column 5, line 57).

Applicants' claimed invention includes prodrugs comprising peptides having a sequence represented by:

$$X_5X_4X_3X_2X_1$$

where X_1 is glutamine, asparagine or tyrosine, X_2 is leucine or lysine, X_3 is serine or lysine, X_4 is serine, isoleucine or lysine, and X_5 is from 0 to 16 amino acids. This sequence includes a cleavage site which shows specificity for PSA and other materials having PSA-specific cleavage. This makes applicants' inventive prodrugs useful for the delivery of cytotoxic agents.

Careful inspection of DeFeo-Jones et al. reveals that this reference does not disclose any of the peptides claimed as being included in applicants' prodrugs, as presented in amended independent claims 19 and 55. All disclosed oligopeptides of DeFeo-Jones et al. are based on one of three "core sequences." The majority of DeFeo-Jones et al.'s oligopeptide sequences are based on a core sequence Lys-Ile-Ser-Tyr-Gln|Ser (SEQ. ID. NO.: 14, where "|" represents the PSA cleavage site in the sequence). Thus, SEQ. ID. NO.: 3, 6-11, 13, 16-44 include either this sequence, or a sequence related to it by a homologous, isosteric, and/or isoelectronic amino acid replacement involving one or more substitutions taken from the table of replacement amino acids in column 4. Another disclosed core sequence is Ile-Ser-Ser-Gln-Tyr|Ser (SEQ. ID. NO.: 2), so that SEQ. ID. NO.: 56-65 are based on this core sequence. A third disclosed core sequence is Gln-Xaa-Ser-Ile-Tyr|Ser (SEQ. ID. NO.: 15, where Xaa is any natural amino acid), so that SEQ. ID. NO.: 4, 5, and 45-53 are based on this core sequence. Thus, the claimed prodrugs are not anticipated by DeFeo-Jones et al.

Merck discloses essentially the same amino acid sequences as DeFeo-Jones et al., as well as a few more. The same three core sequences are presented as in DeFeo-Jones et al. The vast majority of sequences described in the specification (SEQ ID. NO.: 3, 6, 10-11, 13-14, 16-44, 70, 73-75, 78-79, 81-82, 84-87, 89, 92-93, 94-98, 117-121, 124, 128-130, 132-136, and 139-146) contain the core sequence Ser-Tyr-Gln|Ser, and represent longer and/or substituted versions of this sequence. Substitutions are those listed in the table listed on page 10, line 26 to page 11, line 9. A second core sequence (containing Ser-Gln-Tyr|Ser) is represented by SEQ ID NO.: 2, 46, and 57-65. A third core sequence (containing Ser-Ile-Tyr|Ser) is represented by SEQ ID NO.: 4-5, 15, 45, and 47-56. Another small group contains Ser-Tyr-Tyr|Ser and its variants (SEQ. ID NO.: 92-93, 127, 131, and 137-138). None of the Merck sequences anticipate those used in the applicants' claimed prodrug compositions.

Merck does disclose, in SEQ ID NO.: 106, the sequence Ser-Lys-Gln-Ser-Ser-Thr-Glu. This sequence does not read on applicants' claimed prodrugs, even if applicants' amino acid positions of $X_5X_4X_3X_2X_1$ are used to map the Merck peptide. The Merck peptide lacks the X_4 amino acid required by all of applicants' claims.

Neither DeFeo-Jones et al. nor Merck anticipates the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection.

C

Rejection under 35 U.S.C. §103(a) over DeFeo-Jones et al. or Merck

Claims 19-20, 22, 27-29, 32-40, and 59-65 have been rejected as obvious over DeFeo-Jones et al. or Merck. Applicants respectfully traverse the rejections for the following reasons.

DeFeo-Jones et al. and Merck do not suggest the claimed prodrugs or provide motivation to one of skill in the art to make the claimed prodrugs utilizing the recited peptides. The present invention claims PSA-cleavable prodrugs containing peptides which are not related to the peptides of DeFeo-Jones et al. or Merck by way of any equivalent amino acid replacement taught by these references or known in the art. Thus, although DeFeo-Jones et al. and Merck provide tables listing replacement amino acids (column 4 of DeFeo-Jones et al., page 11 of Merck), replacement of any of the oligopeptides of these references with any suggested replacements does not yield a peptide used in a claimed prodrug. One of skill in the art would not be guided by either DeFeo-Jones et al. or Merck to produce the claimed prodrugs.

The peptides disclosed in DeFeo-Jones and Merck are based on the identified PSA cleavage sites in semenogelin I (DeFeo-Jones et al. at col. 2, lines 53-63, Examples 1 and 6; Merck at page 4, lines 7-15, Examples 1 and 6). The claimed invention, on the other hand, includes oligomers derived from analysis of PSA protease-specific cleavage sites in semenogelin II. Neither DeFeo-Jones et al. nor Merck disclose, or suggest that PSA protease-specific semenogelin II cleavage sites would useful for generating possible PSA-cleavable polypeptides, such as those invented by applicants, and used in their inventive prodrugs.

Additionally, each and every oligopeptide disclosed or mentioned in DeFeo-Jones et al. and Merck includes either a serine or threonine residue (disclosed as a replacement for serine in column 4, line 37) immediately to the right of where the oligopeptide is to be proteolytically cleaved by PSA. Neither DeFeo-Jones et al. nor Merck discloses that any other natural amino acid will be suitable at this position. Further, the fact that all of their oligopeptides utilize either serine or threonine makes such a conclusion unreasonable. One of skill in the art, with DeFeo-Jones et al. and Merck in hand, would reasonably conclude that either serine or threonine must be present at this position in order that satisfactory PSA-induced cleavage be carried out. Thus, applicant submits that DeFeo-Jones et al. and Merck do not make it obvious for one of skill in

the art to use any amino acid at the X_{-1} position of the claimed prodrugs. Thus, the claimed invention is not obvious in light of DeFeo-Jones et al. or Merck.

Further, DeFeo-Jones et al. does not present data which show the cleavage of any of the peptide-cytotoxic agent conjugates to yield a cytotoxic agent free of peptide, and effective in its cytotoxicity. Fig. 3 of DeFeo-Jones et al. shows the cytotoxicities of 1) doxorubicin, 2) a non-cleavable oligopeptide, and 3) a non-cleavable oligopeptide-doxorubicin conjugate. There is no evidence from this example, or any other of DeFeo-Jones et al. that any efficacious cytotoxic agent is released from the conjugates prepared in the reference.

In contrast, the present application provides full support for claims to prodrug compositions comprising therapeutically active drug and peptide wherein the drug is cleaved from the peptide by a proteolytic enzyme with the proteolytic activity of PSA. Example 17 and Table 6 show the efficacy of the inventive compositions against TSU-Pr1 cells in the presence of PSA.

Merck discloses the sequence Ser-Lys-Gln-Ser-Ser-Thr-Glu as SEQ ID NO.: 106. This sequence is not described in the written description of the invention, as an embodiment of the Merck invention. The reason for this is made clear with reference to Fig. 3B, in which the entry Ac-SKQ-SSTE-amide (L-Number 106) shows that the percentage of peptide cleaved at 4 hours by York PSA is zero. Thus, Merck clearly teaches away from the use of this sequence in a useful PSA-cleavable prodrug. Thus, it could not have been considered obvious for one of skill in the art to base the present invention on sequences including the sequence Ser-Lys-Gln, as applicants have done.

In view of the foregoing, applicant respectfully submits that the claimed invention is not made obvious by either DeFeo-Jones et al. or Merck.

Rejection Under 35 U.S.C. § 103(a) Over Denmeade et al. (Adv. in Pharm., vol. 35, 1996, pp 281-306) in view of DeFeo-Jones et al. or Merck

Claims 19-27, 32-40, 55-56 and 59-65 have been rejected as obvious over Denmeade in view of DeFeo-Jones or Merck. Applicants respectfully traverse the rejection for the following reasons.

Denmeade et al. generally discloses that "the delivery of a prodrug able to selectively kill both proliferating and nonproliferating prostate cells by activation of programmed cell death pathways should be possible without inducing generalized host toxicity. Presently, this possibility is being tested in a series of preclinical *in vitro* and *in vivo* model systems." (Denmeade et al., bridging pp 301-302). There is no specific disclosure which can be viewed as providing any of the limitations required by the presently claimed invention.

The cited references do not anticipate the instant claims, either individually, or taken in any combination suggested or motivated by the art. Applicants respectfully request reconsideration and withdrawal of the rejections.

CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. No fees are believed due. Please apply any other charges or credits to Deposit Account No. 06-1050, with reference to Attorney Docket No. 07265-149003.

Respectfully submitted,

Date: December 14, 2001

George E. Heibel, Ph.D.
Reg. No. 42,648

Fish & Richardson P.C.
45 Rockefeller Plaza, Suite 2800
New York, New York10111
Telephone: (212) 765-5070
Facsimile: (212) 258-2291

Version with markings to show changes made

In the specification:

Paragraph beginning at page 1, line 4 has been amended as follows:

This application claims priority from U.S. Provisional Application Serial No. 60/047,070, filed 5/1/97, [and] U.S. Provisional Application Serial No. 60/080,046, filed March 30, 1998, and is a continuation of United States Application Serial No. 09/081,707, filed May 5, 1998, now issued United States Patent No. 6,265,540.

In the claims:

Claims 19, 55 have been amended as follows:

19. (Twice Amended) --A composition comprising a prodrug, the prodrug comprising

a therapeutically active drug; and

a peptide comprising an amino acid sequence having a cleavage site specific for an enzyme having a proteolytic activity of prostate specific antigen, wherein the peptide is 20 or fewer amino acids in length, wherein the sequence comprises the amino acids

$X_5X_4X_3X_2X_1$,

wherein X_5 is from 0 to 16 amino acids; X_4 is serine, isoleucine, or lysine; X_3 is serine or lysine; X_2 is leucine or lysine; and X_1 is glutamine, asparagine or tyrosine, and

wherein the peptide is linked to the therapeutically active drug to inhibit the therapeutic activity of the drug, and wherein the therapeutically active drug is cleaved from the peptide upon proteolysis by an enzyme having a proteolytic activity of prostate specific antigen (PSA).--

55. (Twice Amended) --A method of producing a prodrug, the method comprising the step of linking

a therapeutically active drug and

a peptide comprising an amino acid sequence having a cleavage site specific for an enzyme having a proteolytic activity of prostate specific antigen, wherein the peptide is 20 or fewer amino acids in length, wherein the sequence comprises the amino acids

$X_5X_4X_3X_2X_1$,

wherein X_5 is from 0 to 16 amino acids; X_4 is serine, isoleucine, or lysine; X_3 is serine or lysine; X_2 is leucine or lysine; and X_1 is glutamine, asparagine or tyrosine, and wherein the linking of the peptide to the drug inhibits the therapeutic activity of the drug.—